REMARKS

This paper is filed in Response to the final Office Action mailed July 20, 2007, and the Advisory Action mailed October 15, 2007. Applicants respectfully request entry of the Response to Final Office Action filed September 19, 2007. It is noted that the claim amendments and new claims submitted herewith are made with respect to the claims after entry of the Response to Final Office Action filed September 19, 2007.

Claims 1, 2, 4, 7 to 16 and 54 to 65 are pending. Claim 10 has been cancelled herein without prejudice. Applicants maintain the right to prosecute claim 10 in any related application claiming the benefit of priority of the subject application. New claims 66 to 78, have been added. Accordingly, upon entry of this paper, claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78 are under consideration

Regarding the Interviews

Applicants thank the Examiner for various discussions held over the past several months during which time all rejections of record were discussed. During the course of the discussions, the Examiner further indicated that the claims allegedly lacked an adequate written description under 35 U.S.C. §112, first paragraph. Although a formal rejection for an inadequate written description under 35 U.S.C. §112, first paragraph was not made in the Office Action mailed July 20, 2007, in order to advance prosecution of the application, Applicants include in this paper remarks traversing the rejection, as well as a Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers corroborating Applicants' position that the claims are adequately described under 35 U.S.C. §112, first paragraph.

Regarding the Claim Amendments

The amendments to the claims are supported throughout the specification or were made to address an informality. In particular, the amendments to claims 1, 7, 8, 54 and 55, to recite a percent identity is supported, for example, at page 13, line 23, to page 14, line 3. The amendments to claims 1, 7, 8, 11, and 54 to 63 to recite "heavy chain variable region" and "light chain variable region" sequences were made to more clearly indicate the identity of the referenced sequence and are also supported, for example, at page 15, lines 23-28. The amendment to claim 9 to recite "SEQ ID NO:3" is supported, for example, by claim 11, as

originally filed. Thus, as the claim amendments are supported by the specification or were made to address an informality, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

New claims 66 to 78 are supported throughout the specification. In particular, claims 66 to 75 are supported, for example, by originally filed claims 1 to 16, and at page 13, line 23, to page 14, line 3. Claims 76 to 78 are supported, for example, by originally filed claims 1 to 16, at page 13, line 23, to page 14, line 3, and at page 22, lines 17-22. Thus, as claims 66 to 78 are supported by the specification, no new matter has been added and entry thereof is respectfully requested.

I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

The rejection of claims 1, 2, 4, 7 to 15 and 54 to 65 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. According to the Patent Office, allegedly the specification does not enable the skilled artisan to make and use the invention commensurate in scope with the claims.

Applicants respectfully note that this rejection was addressed in the Response to Final Office Action filed September 19, 2007. For the sake of unity and completeness, Applicants reiterate the remarks, as modified to apply to claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78 upon entry of this paper. and in light of the corroborating Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers, as set forth below.

The proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988).

Here, in view of the guidance in the specification and knowledge in the art regarding antibody structure and function at the time of the invention, and that antibody variants and functional fragments having the requisite activity could be produced and identified using routine methods disclosed in the specification or that were known in the art at the time of the invention,

one skilled in the art could make and use the claimed antibodies and functional fragments comprising a sequence at least 75% identical to the amino acid sequence of SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and a sequence at least 75% identical to the amino acid sequence of SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.), and heavy and light chain sequences of SEQ ID NO:1 and SEQ ID NO:3, without undue experimentation.

As pointed out in Applicants' previous Response, the level of knowledge with respect to antibody structure and function was high at the time of the invention. In particular, knowledge regarding antibody structure and function, such as native antibodies having two heavy and light chain sequence, the presence and contribution of three CDRs to binding, and the role of framework regions (FRs) was acknowledged by the Examiner in the Office Action mailed January 3, 2007 (see pages 5 and 6). The specification discloses the function of antibody heavy and light chain variable regions (page 17, line 28, to page 18, line 20). The role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding were also well understood by the skilled artisan at the time of the invention. Consequently, the level of knowledge in the art with respect to antibody structure and function at the time of the invention was high.

Because the level of knowledge in the art with respect to antibody structure and function was high at the time of the invention, such as the sequences that contribute to antigen binding of antibodies (e.g., CDRs and FRs), the skilled artisan would know residues of SEQ ID NO:1 and SEQ ID NO:3 that would be amenable to substitution and would therefore be able to predict with reasonable certainty antibody variants of SEQ ID NO:1 and SEQ ID NO:3 that would have at least partial cell binding activity. As a non-limiting example illustrating this point, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, of SEQ ID NO:1 or SEQ ID NO:3, particularly a conservative substitution outside of a CDR or FR region would likely not destroy binding activity. Thus, the skilled artisan could make a conservative amino acid substitution outside of a CDR or FR with reasonable certainty that the substituted sequence would retain at least partial activity of a non-substituted sequence. Given the large number of amino acids outside the CDR and FR regions, as well as the large number of amino acids outside of antibody variable regions, clearly many variants produced would have at least partial cell binding activity of non-variant SEQ ID NO:1 or SEQ ID NO:3. As an additional non-limiting example illustrating this point, the skilled artisan would know that given

the contribution of CDRs to antigen binding a large number of non-conservative amino acid substitutions in the CDRs of SEQ ID NO:1 or SEQ ID NO:3 would likely reduce or eliminate binding. Thus, the skilled artisan would know not to introduce a large number of non-conservative substitutions or delete a large number of amino acids of the CDRs of SEQ ID NO:1 or SEQ ID NO:3. Consequently, in view of the guidance in the specification and the high level of knowledge in the art regarding antibody structure and function, the skilled artisan would know of general regions and particular residues that would be more or less amenable to substitution and could therefore predict variants and fragments that are likely to have at least partial function of non-variant sequence without actually producing variants and fragments.

In addition to knowing regions and residues that would be more or less amenable to substitution or deletion, the level of skill in the art regarding producing antibodies and functional fragments thereof was also high. For example, conventional methods of producing antibody variants without undue experimentation are disclosed in the specification (page 22, line 16, to page 24, line 9; and page 21, line 16, to page 22, line 14). Such methods include conservative amino acid substitutions at pre-determined locations (page 23, line 23, to page 24, line 9). Furthermore, methods of producing antibody fragments (*e.g.*, Fv, Fab, Fab' and $F(ab')_2$) were known in the art and were routine at the time of the invention (*e.g.*, using recombinant techniques). Methods of identifying which antibody variants and fragments have the recited cell binding and other activities without undue experimentation are also taught by the specification and were also known in the art at the time of the invention. In particular, methods for measuring antibody binding to the recited cell lines and ascertaining cell proliferation and apoptosis are disclosed in the specification (page 44, Example 3, to page 49, Example 6). Thus, in view of the guidance in the specification and the high level of skill in the art at the time of the invention regarding producing antibodies and functional fragments, one skilled in the art could make and use the claimed antibodies and functional fragments comprising a sequence at least 75% identical to the amino acid sequence of SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and a sequence at least 75% identical to the amino acid sequence of SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.), and heavy and light chain sequences of SEQ ID NO:1 and SEQ ID NO:3, without undue experimentation.

Moreover, Applicants also respectfully point out that if the skilled artisan wished to produce antibody variants and functional fragments, producing recombinant proteins was routine

in the art at the time of the invention, and the specification discloses routine assays for identifying antibodies that bind to the recited cell types, as well as cell proliferation/apoptosis assays. Analogous to *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation, given that 1) producing antibody variants and fragments was routine at the time of the invention; and 2) cell binding assays were routine at the time of the invention, undue experimentation would not be required to identify which antibody variants and fragments of SEQ ID NO:1 and SEQ ID NO:3 bind to the recited cell types. Thus, enablement under 35 U.S.C. §112, first paragraph does not require that every amino acid of a given protein, such as an antibody, be analyzed so that the skilled artisan knows or is able to predict with absolute certainty the effect of a substitution or deletion *a priori.* Consequently, there is no need to "predict" in advance antibody variants and fragments of SEQ ID NO:1 and SEQ ID NO:3 that bind to the recited cell types in order to obtain antibody variants and functional fragments of SEQ ID NO:1 and SEQ ID NO:3. In view of the foregoing, the skilled artisan could produce antibody variants and functional fragments of SEQ ID NO:1 and SEQ ID without knowing in advance the effect of particular substitutions or deletions on activity NO:3

Finally, the number of antibody variants and functional fragments encompassed by claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78 are limited as they are required to have at least some degree of binding to the recited cell lines and therefore do not include inoperative embodiments. The antibodies and functional fragments are further limited in number because of the high degree of sequence identity among members, namely they have a sequence at least 75% identical to the amino acid sequence of SEQ ID NO:1 and a sequence at least 75% identical to the amino acid sequence of SEQ ID NO:3. Moreover, because the antibodies and functional fragments encompassed by claims are required to exhibit binding to at least one of the recited cell lines it is clear that there will be three CDRs regions with flanking FR regions in each of the heavy and light chain sequences. Thus, the number of antibodies and functional fragments encompassed by the claims will necessarily be limited based upon the structural and functional requirements of antibodies discussed above (e.g., three CDRs regions with flanking FR regions in each heavy and light chain sequence), the high degree of sequence identity with SEQ ID NO:1 and SEQ ID NO:3, and the requirement of at least partial cell binding activity. Consequently, in view of the

structural and functional requirements of antibodies, the number of antibodies and functional fragments encompassed by the claims will be limited.

In terms of claims 64 and 65, these claims are directed to antibody heavy and light chain variable region sequences. Applicants recognize that a light chain variable region or a heavy chain variable region by itself may not bind to antigen. However, the proper standard for enablement under 35 U.S.C. §112, first paragraph is whether or not the skilled artisan could make and use the sequences of claims 64 and 65 without undue experimentation. Thus, provided that the skilled artisan could make and use SEQ ID NO:1 and SEQ ID NO:3 without undue experimentation, claims 64 and 65 are adequately enabled under 35 U.S.C. §112, first paragraph, regardless of whether SEQ ID NO:1 or SEQ ID NO:3 binds antigen.

Here, one skilled in the art could readily make and use heavy and light chain variable region sequences SEQ ID NO:1 and SEQ ID NO:3 of claims 64 and 65 without undue experimentation. For example, as disclosed in the specification, each of SEQ ID NO:1 and SEQ ID NO:3 could be recombinantly or synthetically produced without undue experimentation (see, page 21, line 16, to page 22, line 14). In particular, for example, as disclosed in the specification, each of SEQ ID NO:1 and SEQ ID NO:3 could be linked in order to form small antigen binding fragments (see, page 18, lines 4-9). In addition, each of SEQ ID NO:1 and SEQ ID NO:3 could be expressed in a eukaryotic or prokaryotic cell line in order to produce an antibody that contains SEQ ID NO:1 and SEQ ID NO:3 without undue experimentation, as disclosed in the specification (see page 21, lines 16-19). Methods of producing heavy and light chain sequences for antibodies by expressing such sequences were known in the art and routine at the time of the invention (see, e.g., Antibody Engineering, Roland Kontermann (Editor), Springer Lab Manuals, May 18, 2001; Recombinant Antibodies, Frank Breitling and Stefan Dübel, Wiley-Spektrum, September 30, 1999). Consequently, as SEQ ID NO:1 and SEQ ID NO:3 could be made and used without undue experimentation at the time of the invention, claims 64 and 65 are adequately enabled.

In addition, the accompanying Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers corroborates Applicants' position that the claims are adequately enabled under 35 U.S.C. §112, first paragraph. In particular, among other things Dr. Vollmers declares and states at paragraph 20 of the Declaration that:

1) Antibodies and functional fragments could be produced in view of the guidance in the specification and knowledge in the art at the time of the invention. For example, producing recombinant proteins was routine in the art at the time of the invention. Methods of producing sequence variants including conservative amino acid substitutions at pre-determined locations are disclosed in the specification (page 22, line 17, to page 24, line 9). Additional methods for producing antibodies were known in the art at the time of the invention (see, for example, A Practical Guide to Monoclonal Antibodies by J. Eryl Liddell (Author), A. Cryer (Author), John Wiley & Sons, 1991); and

2) Methods of identifying antibody variants that have binding activity without undue experimentation were also known in the art and are also disclosed by the specification. In particular, the specification discloses routine assays for identifying antibodies that bind to the recited cell types, and methods for ascertaining cell proliferation and apoptosis, are disclosed in the specification (page 44, example 3, to page 49 line 5). Additional methods for screening antibodies for binding activity were known in the art at the time of the invention (see, for example, A Practical Guide to Monoclonal Antibodies by J. Eryl Liddell (Author), A. Cryer (Author), John Wiley & Sons, 1991).

In view of the foregoing, one skilled in the art could readily produce antibodies and functional fragments that comprise heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and light chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.), and wherein the heavy or light chain variable region sequence has an insertion or deletion of one amino acid residue, that retain at least partial binding activity, without undue experimentation. Accordingly, claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78 are adequately enabled and Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

II. THE CLAIMS COMPLY WITH THE REQUIREMENTS OF 35 U.S.C. §112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

As stated above, during the course of various discussions with the Examiner it was alleged by the Examiner that the claims lacked an adequate written description under 35 U.S.C. §112, first paragraph. Although no formal rejection under 35 U.S.C. §112, first paragraph, written description is pending, in order to advance prosecution of the application, Applicants

include the following remarks traversing such a rejection if applied to claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78.

The claims as originally filed, prior to entry of this paper, and following entry of this paper are adequately described under 35 U.S.C. §112, first paragraph. In particular, in view of the guidance in the specification, which discloses antibody variable heavy and light chain variable region sequences (e.g., SEQ ID NOs:1 and 3), the high level of knowledge and skill in the art regarding antibody structure and function, and the high degree of sequence identity of the claimed antibodies and functional fragments to SEQ ID NOs:1 and 3, the skilled artisan would be apprised of antibodies and functional fragments within claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78. Consequently, claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78 are adequately described.

The written description requirement under 35 U.S.C. §112, first paragraph is "to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, F.2d 588, 592 (CCPA 1977). A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The description needed to satisfy the requirements of 35 U.S.C. §112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.....Since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of the knowledge in the field and differences in the predictability of the science....the law must take cognizance of the scientific facts." *Capon v. Eshhar*, 418 F.3d , 1349, 1357 (Fed. Cir. 2005). Thus, an adequate written description is a factual inquiry measured by one of ordinary skill in the art, that varies with the nature and scope of the invention, taking into consideration the scientific and technologic knowledge in existence in the relevant field.

Furthermore, to satisfy the written description requirement, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir.

1988). In this regard, "(1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Thus, in view of the standard set by the court, an actual reduction to practice or disclosure of specific examples of antibodies or functional fragments within the scope of the claims is not required under 35 U.S.C. §112, first paragraph.

Particularly relevant to claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78, in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005), the court held that a single embodiment of a protein (a reverse transcriptase (RT)) provided an adequate written description for claims directed to a genus of such proteins since the single disclosed protein embodiment had 1) sufficient correlation between structure and function; and 2) shared significant homology with others. In affirming that the patents in-issue satisfied the written description requirement, as articulated by the court in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (1997) and *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the court held that "the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features—DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient. In short, there is no error in the district court's ruling that the claims in the patents-in-suit satisfy the written description requirement of §112." Thus, the claims of the patents in-issue in *Invitrogen*, which were not limited by reciting a particular amount of homology or identity to a reference sequence in the claims, were held to satisfy the written description requirement even though there was only a single disclosed embodiment. Accordingly, in view of *Invitrogen* a single embodiment provides a written description for a genus of proteins where there is sufficient correlation between protein structure and function, and the members of the species share significant homology.

Here, the skilled artisan has substantial understanding of antibody structure and function, and the claimed antibodies and functional fragments share significant sequence homology with heavy and light chain variable region sequences SEQ ID NOs:1 and 3 (at least 75% identical to

SEQ ID NOs:1 and 3). Furthermore, the specification discloses a working example having binding activity within the genus. Consequently, given that the recited sequences share significant sequence homology, the correlation between antibody structure and function, and that the specification discloses an embodiment within the genus having binding activity, clearly the claims meet the written description standard as articulated by the court in *Invitrogen*.

As discussed above, the specification teaches antibody heavy and light chain variable sequences (e.g., SEQ ID NOs:1 and 3), and that such sequences were derived from a human antibody. As also discussed above, the level of knowledge and skill in the art with respect to antibody structure and function was high at the time of the invention. Evidence of such knowledge regarding antibody structure and function, such as antibodies having heavy and light chain variable and constant region is taught by the specification (page 17, line 25, to page 18, line 10; page 15, line 3). The role of variable region sequences, including CDRs in antigen binding was understood by the skilled artisan at the time of the invention, as acknowledged in the Office Action (see, for example, pages 2-3 of the Office Action) and published throughout the scientific literature at the time of the invention. The position of CDRs in antibody variable region sequences is predictable using techniques known at the time of the invention (see, for example, Morea *et al.*, Methods 20:267 (2000)). A sequence alignment with a database of known human immunoglobulin sequences (e.g., IMGT, see the specification page 44, lines 9-20) can localize CDRs. Consequently, the level of knowledge and skill in the art concerning antibody structure and function at the time of the invention was high. Thus, in view of the high degree of knowledge and skill in the art concerning antibody structure and function at the time of the invention, combined with the guidance in the specification of the heavy and light chain variable sequences, SEQ ID NOs:1 and 3, the ability to predict locations of CDRs, and the significant sequence identity of the antibodies and functional fragments to SEQ ID NOs:1 and 3, the skilled artisan would know a number of antibodies and functional fragments within claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78.

As an illustration, the skilled artisan would know that a non-conservative or conservative substitution outside a CDR or FR of either SEQ ID NOs:1 or 3 would retain at least partial antigen binding activity. Given the large number of amino acids outside of CDRs and FRs and the large number of amino acids outside of variable regions clearly the skilled artisan could readily envision a number of variants within the scope of the claims that have at least partial

antigen binding activity of SEQ ID NOs:1 and 3. Conservative substitutions within a CDR or FR region of SEQ ID NOs:1 or 3 would also likely not destroy binding activity of an antibody. Consequently, the skilled artisan would be apprised of a number of antibodies and antigen binding fragments within the scope of claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78.

The accompanying Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers corroborates that the claims are adequately described under 35 U.S.C. §112, first paragraph. Dr. Vollmers provides objective facts, and conclusions based upon the objective facts, in the accompanying Declaration.

Concerning antibodies and functional fragments that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:1 and a light chain variable region sequence at least 75% identical to SEQ ID NO:3, Dr. Vollmers declares and states at paragraphs 6 to 15 of the Declaration that:

One skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and functional fragments that specifically bind to at least one of the recited cell lines as recited, and (i) that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:3; (ii) that comprise a heavy chain variable region sequence at least 80% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 80% identical to SEQ ID NO:3; (iii) that comprise a heavy chain variable region sequence at least 85% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 85% identical to SEQ ID NO:3; (iv) that comprise a heavy chain variable region sequence at least 90% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 90% identical to SEQ ID NO:3; or (v) that comprise a heavy chain variable region sequence at least 95% identical to SEQ ID NO:1, and comprise a light chain variable region sequence at least 95% identical to SEQ ID NO:3.

Dr. Vollmers' conclusions are based upon the following objective facts: The specification discloses the heavy chain variable region amino acid sequence, SEQ ID NO:1, and the light chain variable region amino acid sequence, SEQ ID NO:3 (Figures 1 and 2). The specification discloses that heavy and light chain variable region sequences SEQ ID NOs:1 and 3 are derived from a human antibody (Example 2; see also, page 15, lines 23-28; and page 17, lines 7-13). The

location of the CDRs in antibody variable region sequences is predictable using techniques known at the time of the invention (see, for example, Morea *et al.*, Methods 20:267 (2000)). A sequence alignment with a database of known human immunoglobulin sequences (e.g., IMGT, see the specification page 44, lines 9-20) can localize the CDRs. Dr. Vollmers therefore concludes that the skilled artisan would know the location of the three CDRs in heavy chain variable region sequence SEQ ID NO:1 and the location of the three CDRs in light chain variable region sequence SEQ ID NO:3.

Dr. Vollmers furthermore declares that as the locations of the three CDRs in SEQ ID NOs:1 and 3 would be known to the skilled artisan and that SEQ ID NOs:1 and 3 are derived from a human antibody, the skilled artisan would also have known the location of the framework regions (FRs) in SEQ ID NOs:1 and 3, as well as the D- and J-regions in SEQ ID NOs:1 and 3. Dr. Vollmers therefore declares that the skilled artisan would know the majority of amino acid residues of SEQ ID NOs:1 and 3 that contribute to antigen binding.

Dr. Vollmers declares that the level of knowledge and skill in the art concerning antibody structure and function at the time of the invention was high. As evidence of the high level of knowledge and skill in the art, the specification discloses the function of antibody heavy and light chain variable and constant regions (page 17, line 25, to page 18, line 10; page 15, line 3). The role of variable region sequences, including CDRs in antigen binding was well known to the skilled artisan at the time of the invention, as acknowledged in the Office Action (see, for example, pages 2-3 of the Office Action).

Dr. Vollmers also declares that because the amino acids of heavy and light chain variable region sequences SEQ ID NOs:1 and 3 that contribute to antigen binding would be known to one of skill in the art, and the level of knowledge and skill in the art concerning antibody structure and function was high, the skilled artisan would have known antibodies and functional fragments with amino acid residues of SEQ ID NOs:1 and 3 that could be substituted (i.e., would likely not destroy binding activity), and therefore would envision heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:1, and light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:3 that would have at least partial activity.

Dr. Vollmers illustrates this point by way of the example of an amino acid substitution. In brief, an amino acid substitution such as a non-conservative or conservative substitution

outside a CDR or FR region of SEQ ID NOs:1 or 3 would likely not destroy binding activity of an antibody, and conservative substitutions within a CDR or FR region of SEQ ID NOs:1 or 3 would also likely not destroy binding activity of an antibody. Dr. Vollmers thus declares that the skilled artisan would know with a high degree of confidence that an antibody comprising SEQ ID NO:1 or 3 with a non-conservative or conservative substitution located outside of a CDR or FR of SEQ ID NO:1 or 3, or a conservative substitution within a CDR or FR of SEQ ID NO:1 or 3, would very likely retain at least partial binding activity.

Dr. Vollmers points out that typically about 50% of the amino acids in a given heavy or light chain variable region sequence are not within one of the three CDRs. Dr. Vollmers concludes that because there are a large number of amino acids outside of the CDRs, antibody variants that likely retain at least partial binding activity would be readily envisioned by the skilled artisan. Thus, Dr. Vollmers declares that the skilled artisan would also readily envision antibodies and functional fragments with heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:1, and light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:3, that would retain at least partial binding activity without actually having to test the particular variant.

Dr. Vollmers further declares that not only would the skilled artisan envision antibodies and functional fragments with heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:1, and light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:3, but would also know that, by contrast, introducing a large number of non-conservative substitutions, insertions or deletions into the CDRs of SEQ ID NOs:1 or 3 would likely result in destroying binding activity. For example, the skilled artisan knows that heavy chain variable region CDR3 appears to be important to confer fine binding specificity (see, for example, Chen et al., J. Immunol. 147:2359 (1991)). Thus, Dr. Vollmers concludes that the skilled artisan would also know that a large number of non-conservative substitutions, insertions or deletions of heavy chain variable region CDR3 would likely result in loss of antigen specificity, and therefore, would also readily envision SEQ ID NOs:1 and 3 with sufficient substitutions, insertions or deletions such that the antibody or functional fragment would be unlikely to have binding activity.

Dr. Vollmers moreover declares that the ability of the skilled artisan to envision sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:1 and

sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:3 that would retain at least partial binding activity is further evidenced by the fact that the process of humanizing antibodies was well known to the skilled artisan at the time of the invention (see, for example, U.S. Patent No. 6,180,370). For example, Dr. Vollmers points out that grafting non-human CDRs to human framework sequences and combining them with human constant region sequences was well established at the time of the invention. Dr. Vollmers thus concludes that because all CDRs of a given variable region sequence could be transferred from one mammalian species to another without destroying binding activity of the resultant humanized antibody, the skilled artisan could readily envision antibodies and functional fragments that comprise heavy chain variable region sequences with 75% or more identity to SEQ ID NO:1, and light chain variable region sequences with 75% or more identity to SEQ ID NO:3. Moreover, Dr. Vollmers declares that given that humanized antibodies retain binding, variable region sequences can include non-identical amino acids in many positions outside of the CDRs without destroying binding activity, and therefore can be substantially non-identical to SEQ ID NOs:1 and 3 outside of the CDRs. Dr. Vollmers thus concludes that the skilled artisan would readily envision a number of antibodies and functional fragments that vary in positions outside of the CDRs of SEQ ID NOs:1 and 3 that retain at least partial binding activity.

To corroborate Dr. Vollmers' conclusions concerning substitutions within CDRs, submitted herewith as Exhibit A is a publication by Kipriyanov et al. (Protein Engineering 10:445 (1997)). In Exhibit A the authors report that a substitution of a cysteine residue by a serine within CDR3 of an antibody heavy chain variable region did not have an adverse effect on affinity. Thus, Exhibit A corroborates that substitutions within CDRs can be tolerated.

To corroborate Dr. Vollmers' conclusions concerning substitutions within FRs, submitted herewith as Exhibit B is a publication by Holmes *et al.* (J. Immunol. 167:296 (2001)). The authors of Exhibit B report several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity. Thus, Exhibit B corroborates that substitutions of an FR residue can be tolerated.

Concerning antibodies and functional fragments that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:1 and a light chain variable region sequence at least 75% identical to SEQ ID NO:3, wherein the heavy or light chain variable

region sequence has an insertion or deletion of one amino acid residue, Dr. Vollmers declares and states at paragraphs 16 to 19 of the Declaration that:

One skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and functional fragments that specifically bind to at least one of the recited cell lines and that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:1 and a light chain variable region sequence at least 75% identical to SEQ ID NO:3, wherein the heavy or light chain variable region sequence has an insertion or deletion of an amino acid residue (paragraph 16).

Dr. Vollmers' conclusions are based upon the following objective facts: again, the majority of amino acids of SEQ ID NOs:1 and 3 that contribute to antigen binding would be known, and the level of knowledge and skill in the art concerning antibody structure and function was high. Consequently, the skilled artisan would have known amino acids of SEQ ID NOs:1 and 3 that could be substituted (i.e., would likely not destroy binding activity), and therefore would envision heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:1, and light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:3 that would have at least partial activity. In addition, an amino acid insertion or deletion of SEQ ID NOs:1 or 3 would also likely not destroy binding activity of an antibody (paragraph 18).

To corroborate Dr. Vollmers' conclusions concerning insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, which occurs during antibody affinity maturation, submitted herewith as Exhibit C is a publication by Wilson *et al.* (J. Exp. Med. 187:59 (1998)). The authors of Exhibit C report a number of insertions and deletions of variable heavy chains that occur naturally during affinity maturation. Thus, Exhibit C corroborates that insertions and deletions of SEQ ID NO:1 or 3 would very likely retain at least partial binding activity.

To further corroborate Dr. Vollmers' conclusions concerning insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, submitted herewith as Exhibit D is a publication by Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002)) The authors of Exhibit D report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated. Thus, Exhibit D corroborates

that a heavy or light chain variable region sequence insertion or deletion, even within a CDR, can be tolerated (paragraph 19).

In sum, in view of the guidance in the specification and the substantial understanding of antibody structure and function at the time of the invention, and the degree of sequence identity of the claimed antibodies and functional fragments to SEQ ID NOs:1 and 3, as corroborated by the accompanying Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers and Exhibits A-D, the skilled artisan would be apprised of a number of antibodies and functional fragments within claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78. Furthermore, in view of the substantial understanding of antibody structure and function, the significant sequence homology to SEQ ID NOs:1 and 3 required by the claims, and that the specification discloses an embodiment having activity, clearly the claims meet the standard for written description articulated by the court in *Invitrogen*. Consequently, Applicants respectfully state that claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78 are adequately described to one skilled in the art, and therefore satisfy 35 U.S.C. §112, first paragraph as providing an adequate written description.

III. REJECTION UNDER 35 U.S.C. §102(a)

The rejection of claims 1, 2, 4, 7 to 16 and 54 to 65 under 35 U.S.C. §102(a) as allegedly anticipated by Brandlein *et al.* (Human Antibodies 11:107 (2002)) is respectfully traversed.

Applicants respectfully note that this rejection was addressed in the Response to Final Office Action filed September 19, 2007. For the sake of unity and completeness, Applicants reiterate the remarks, as set forth below.

Claims 1, 2, 4, 7 to 16 and 54 to 65 are not anticipated under 35 U.S.C. §102(a) in view of Brandlein *et al.* (Human Antibodies 11:107 (2002)). In this regard a certified English translation of German priority application DE 10210427.1, filed March 9, 2002, was submitted with the Response to Final Office Action filed September 19, 2007. Accordingly, in view of the submission of the certified English translation of DE 10210427.1, the claims of the subject application are entitled to a March 9, 2002 priority date.

Brandlein *et al.* (Human Antibodies 11:107 (2002)) was not published prior to March 9, 2002. In this regard, a copy of an email received from Ms. Susan Hendriks, Marketing Coordinator at IOS Press, the publisher of Human Antibodies was submitted with the Response to Final Office Action filed September 19, 2007 (labeled as Exhibit A). In Exhibit A Ms.

Hendriks stated that "Volume 11, number 4 of Human An[it]tibodies was published on April 18th 2003." (see Exhibit A submitted with the Response to Final Office Action filed September 19, 2007) Thus, as Brandlein *et al.* (Human Antibodies 11:107 (2002)) was not published prior to March 9, 2002, it is not available as prior art. Consequently, Applicants respectfully request that the rejection under 35 U.S.C. §102(a) be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

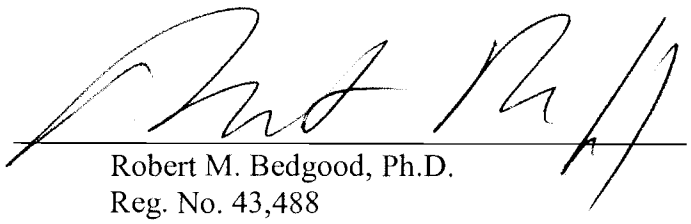
If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP

Date: April 16, 2008



Robert M. Bedgood, Ph.D.
Reg. No. 43,488

Customer No. 25700
12255 El Camino Real, Suite 300
San Diego, CA 92130-2006
Telephone: (858) 509-4065
Facsimile: (858) 509-4010